Emergency management of diabetic ketoacidosis in adults

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The authors propose a regimen for managing diabetic ketoacidosis in adults based on available evidence and their experince in the emergency department.

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D iabetic ketoacidosis (DKA) is a potentially fatal metabolic disorder presenting most weeks in most accident and emergency (A&E) departments.[1] The disorder can have significant mortality if misdiagnosed or mistreated. Numerous management strategies have been described. Our aim is to describe a regimen that is based, as far as possible, on available evidence but also on our experience in managing patients with DKA in the A&E department and on inpatient wards.

A literature search was carried out on Medline and the Cochrane Databases using "diabetic ketoacidosis" as a MeSH heading and as text-word. High yield journals were hand searched. Papers identified were appraised in the ways described in the Users' guide series published in *JAMA*.

We will not be discussing the derangements in intermediary metabolism involved, nor would we suggest extrapolating the proposed regimen to children. Although some of the issues discussed may be considered by some to be outwith the remit of A&E medicine it would seem prudent to ensure that A&E staff were aware of the probable management of such patients in the hours after they leave the A&E department.

AETIOLOGY AND DEFINITION

DKA may be the first presentation of diabetes. Insulin error (with or without intercurrent illness) is the most common precipitating factor, accounting for nearly two thirds of cases (excluding those where DKA was the first presentation of diabetes mellitus).[2]

The main features of DKA are hyperglycaemia, metabolic acidosis with a high anion gap and heavy ketonuria (box 1). This contrasts with the other hyperglycaemic diabetic emergency of hyperosmolar non-ketotic hyperglycaemia where there is no acidosis, absent or minimal ketonuria but often very high glucose levels (>33 mM) and very high serum sodium levels (>150 mM).[3]

DIAGNOSIS

Clinical findings

There are no specific clinical signs that confirm or refute the diagnosis of DKA. The diagnosis is comparatively straight forward where there is a clear history that the patient has diabetes but can cause serious diagnostic difficulty where the patient is unconscious or DKA is the first presentation of diabetes (a past history of diabetes mellitus will be absent in 1 in 10 patients). The possibility of DKA (or other metabolic acidosis) should be considered whenever assessing a patient who presents with "hyperventilation"[4] and it is always essential to measure the blood glucose early in the resuscitation of any unconscious patient.

Polyuria, polydipsia, and weakness are usually present. Nausea, vomiting, or abdominal pain may predominate. If the patient is already being treated with insulin, there may be a history of reduced or omitted insulin. Chest pain may be described if DKA complicates acute myocardial infarction, although silent infarction may occur.

On examination the patient has an increased depth and rate of respiration. The mouth, tongue and lips are dry. The majority of doctors can smell ketones on the patient's breath but this is an unreliable sign. There may be other signs of volume depletion. Signs of infection (for example, lobar pneumonia) should be sought; absence of fever does not exclude infection.

Bedside tests

A capillary glucose measurement should be made (ensure there is no sugar on the skin where skin prick is made).

Defining DKA as serum glucose >250 mg/dl (>14 mM), metabolic acidosis with corrected pH<7.30 or serum bicarbonate <15 mM and ketonaemia, the sensitivity of urine ketone dip test for ketonaemia in patients with DKA is 97% (95% CI 92% to 99%).[5] The absence of ketonuria makes the diagnosis of DKA unlikely. It is possible that clinical staff in the study were using negative urine dip stick test to rule out DKA; the study would therefore overestimate its sensitivity. Few laboratories offer an urgent ketone level; an estimate of the severity of ketonaemia can be made from the anion gap (available immediately on some "blood gas analysers"); an anion gap >20 mM is abnormal.

Acute myocardial infarction can precipitate DKA. A 12 lead ECG should be recorded.

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> **Box 1 The usual features of diabetic ketoacidosis**
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> - Hyperglycaemia (>14 mM).
> - Metabolic acidosis (pH<7.35 and bicarbonate <15 mM).
> - High anion gap.
> - Ketonaemia/heavy (3+) ketonuria.

Special tests

It is not necessary to take arterial blood as a routine in suspected DKA; venous blood can be sampled in a pre-heparinised syringe and then analysed with a "blood gas analyser". The mean difference between arterial and venous pH in DKA is 0.03 (CI not given in text, but in only 1 case of 44 was the difference greater than 0.1).[6] Arterial sampling should be reserved for cases when respiratory failure is suspected.

Despite a significant reduction in total body potassium, the serum concentration is usually normal or high at presentation because of a shift into the extracellular compartment. The steepest decline of [potassium] occurs in the first few hours of treatment; many recommend that values are checked at least hourly during this phase.

Venous glucose should be measured hourly. Management should be based on capillary glucose measurements only after these have been found to agree with venous levels (at presentation the degree of hyperglycaemia may render the capillary measurement inaccurate).

Leucocytosis is usual and should not be interpreted as a sign of infection. Routine treatment with antibiotics is not indicated; blood and urine should be cultured.

TREATMENT

DKA is a complex life threatening problem and the management should not be left to inexperienced staff. There should be early consultation between A&E staff and specialist diabetes teams. Patients with DKA need four things;

- Fluid
- Insulin
- Potassium
- Education

Early venous access is essential. In shocked patients large bore cannulas should be sited and standard measures instituted (oxygen, cardiac monitor, regular measurement of pulse and blood pressure). Avoid central lines unless essential for monitoring in severely ill patients. Adjuncts to resuscitation should include a nasogastric tube in patients who are not alert (gastroparesis occurs and aspiration of gastric contents is a complication of DKA). A urinary catheter is needed if patients are haemodynamically unstable and need accurate measurement of urine output.

Hydration

A regimen suitable for patients who are not shocked or oliguric (<30 ml/h) is 500 ml/h of 0.9% saline for four hours followed by 250 ml/h for the next four hours. This is associated with as rapid a correction of acidosis and hyperglycaemia as a regimen using twice these rates.[7] Unnecessarily large volumes of intravenous fluids should be avoided because of the high case fatality rate of cerebral oedema. Physiological (0.9%) saline is the fluid usually used in the initial management of DKA though no formal comparisons with 0.45% saline or Ringer's solution have been reported. Volume status can be assessed on the basis of clinical assessment (such as heart rate and BP), from urine output (a high urine output may indicate only osmotic diuresis but a low urine output should trigger a thorough assessment of renal function and the state of hydration), from urea measurements, and (sometimes) from invasive monitoring.

In patients with significant comorbidity (especially cardiac disease) invasive haemodynamic monitoring may help to guide the rate of fluid replacement. This has not been subjected to prospective evaluation and the potential complications of attempted central cannulation in volume depleted patients should be borne in mind. This is not a group of patients in which to "practise" central cannulation.

Once [glucose] has fallen to around 14 mM (a value based on tradition more than anything else) 5% dextrose (with appropriate potassium) is given rather than saline. Administering hypertonic dextrose (1 litre 10% dextrose + 40 units insulin at 250 ml/h) rather than isotonic dextrose (1 litre 5% dextrose + 10 units insulin at 250 ml/h) may accelerate the clearance of ketone bodies but also causes a rise in [glucose] without an additional improvement in blood pH or bicarbonate.[8]

Insulin

Type of insulin

A soluble insulin is normally used with the aim of permitting more rapid titration of circulating insulin levels (though there are no trial data comparing soluble against other types of insulin). If an intravenous bolus is followed by an intravenous infusion steady state insulin levels are reached very quickly. The half life of circulating insulin is five minutes; use of an intravenous infusion has the advantage over intermittent boluses of permitting a more rapid reduction in insulin level.

Dose of insulin

We usually give a bolus of six units then an infusion of 6 units/h when starting treatment of an adult with DKA (0.1 units/kg for patients who weigh less than 60 kg). Higher doses are associated with an increased risk of hypoglycaemia. A target reduction in [glucose] of 5 mM/h has been suggested though this has not been subjected to evaluation.[9] Rather than using a "sliding scale", we suggest that an infusion rate is started and then reviewed by a doctor every one to two hours (they should be reviewing the patient at least this frequently anyway). This is analogous to reviewing hypotensive or shocked patients frequently rather than prewriting their fluids for several hours.

Failure to achieve a reduction with this regimen for insulin should prompt a check of intravenous access, all connections, and the infusion device. If no mechanical cause is found a

failure to respond may represent untreated infection or inadequate volume replacement. An additional bolus of insulin (equivalent to the previous hourly rate) should be given and the infusion rate doubled.

Conventional insulin infusion rates are often insufficient to achieve normoglycaemia in patients on an adrenaline (epinephrine) infusion because of the antagonistic effects of adrenaline; the insulin infusion rate should be increased until [glucose] falls at the desired rate. There is no unsafe upper limit provided frequent clinical and biochemical reassessment is carried out.

Duration of insulin infusion
Ketone bodies are cleared more slowly than glucose. The insulin infusion should be continued until ketosis and acidosis have cleared. Discontinuing insulin on the basis of (near) normal glucose levels can result in recurrence of ketoacidosis. If, however, the insulin infusion is continued after [glucose] normalises there is a danger of hypoglycaemia unless hypertonic dextrose in infused. The first subcutaneous injection must be given *before* the insulin infusion is stopped; otherwise insulin levels may fall too low and ketoacidosis recur. In most hospitals staffing is better in office hours than out of hours. It may therefore be preferable to change from intravenous to subcutaneous insulin in the morning rather than in the evening.

Potassium
Significant hypokalaemia is the most common life threatening electrolyte derangement that occurs during the treatment of DKA. Intravenous potassium replacement will be required after insulin is given as potassium will move into cells. Potassium replacement should *not* be started *before* insulin treatment; extracellular levels may otherwise rise dangerously high. Potassium replacement should be given as soon as insulin and fluid are started *and* the [K] level is known to be below the upper limit of the reference range. Regimens for potassium supplementation have not been formally evaluated. One suitable regimen for potassium replacement has been proposed[10]:

- Start KCl once [K] is normal or low.
- 20 mmol/h is an average dose; adjust according to hourly levels.
- If the initial level is high, start KCl as soon as level falls into normal range.

Education
Many cases of DKA occur after incorrect reduction or omission of insulin treatment. It is vital that patients who develop DKA receive, before discharge from hospital, education about how to manage their insulin in the event of intercurrent illness. This information should have been provided previously to all patients treated with insulin.

Bicarbonate
Severe acidosis has adverse effects on many organs, especially the brain and the heart. It may, therefore, seem appealing to give bicarbonate as treatment for the metabolic acidosis that occurs in DKA. *There is no evidence to support this*. Studies (not RCTs) have failed to find evidence of faster biochemical recovery with bicarbonate treatment even in severely patients.[11–14] One prospective study found no metabolic benefits from bicarbonate administration and that bicarbonate (1 litre 150 mM sodium bicarbonate over one hour) delayed the fall in total ketone bodies and lactate levels.[15]

Sodium bicarbonate is both hypertonic and hyperosmolar. This can depress cardiac activity and lead to fluid shifts increasing the intravascular volume (which can provoke pulmonary oedema). The increase in pH shifts the Hb-O_2 dissociation curve to the left, potentially decreasing tissue oxygenation and increasing lactate production. Bicarbonate infusions can cause a rise in P_aCO_2; rapid diffusion across cell membranes can actually worsen intracellular acidosis, especially in situations when the patient is unable to compensate by increasing carbon dioxide excretion. During the recovery phase of DKA any lactate produced during tissue hypoxia is metabolised to bicarbonate leading to rebound alkalosis.

Phosphate
Phosphate levels are affected in DKA in much the same way as potassium (that is, extracellular shift but depleted total body levels). A small study found that the addition of phosphate to standard treatment did not reduce the time taken to reach recovery indices of bicarbonate, pH, or glucose.[16] Differences in magnesium and 2,3DPG levels and in P50 (the Pao_2 at which haemoglobin is 50% saturated) were not statistically significant. In another study phosphate supplementation (15 or 45 mmol) did not affect the rate of correction of [glucose], [bicarbonate] or pH.[17]

PROGNOSIS
An overall mortality rate of 3.9% was reported from Birmingham (United Kingdom) for the period 1971 to 1991.[2] Many of these deaths occurred in patients with significant comorbidity; it may not be possible to reduce the mortality rate further. The mortality rate increases with age: 1.9% in those aged 12 to 69 and 19.6% in those aged 70 or more (95% CI for the difference in mortality between the two age groups 9.9% to 25.4%).

If cerebral oedema complicates DKA the mortality rate is over 90%. Although most cases occur in patients younger than 20 years it can occur in older patients. Avoiding falls in osmolality greater than 5 mosm/h has been suggested as a way of reducing the likelihood of developing cerebraloedema.[9]

FUTURE DEVELOPMENTS
There are insulin analogues (Aspart and LisPro) that are ultra-fast acting insulins with shorter half lives than soluble insulins currently in use. There is no evidence that the use of such insulins increases the risk of DKA and the management of patients with diabetes treated with these agents is no different from that outlined above.

Continuous subcutaneous insulin infusions are commonly used in continental Europe to treat type I diabetes mellitus and their use is increasing in the UK. They were initially associated with an increased risk of DKA because of equipment failure.[18] [19] As the technology has improved this risk has fallen. Treatment of DKA in patients usually treated with continuous subcutaneous insulin infusions does not differ from the conventional approach.

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